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September 10, 1999

Dockets Management Branch (HFA-305)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket # 99N-0193-Supplemental and Other Changes to an Approved Application

Dear Sir or Madam:

Below are SST's comments with respect to the above sited proposed rule published for public comment on June 28,1999. SST is the US representative for API and pharmaceutical intermediate manufacturers worldwide. As such, we are very interested in the proposed rule and how it will effect the companies we represent. We greatly appreciate the opportunity to comment on this rule. Our comments are all of a general nature and we hope they will be thoughtfully considered.

1. The proposed Rule and accompanying Guidance document regarding changes to an approved application focuses overwhelmingly on drug product manufacturing. It is implied, via lack of other documentation, that this Rule and Guidance are intended to apply to drug substance manufacturing as well. However, the processes used in drug product and drug substance manufacturing differ greatly, and so, it is often difficult to determine how the changes outlined for drug products apply to drug substances. It is our belief that a separate document addressing changes related to an approved application for a drug substance should be developed. The development of such a document would serve to help avoid the confusion generated when trying to apply the existing proposed Rule and Guidance to a drug substance issue. We feel this belief is supported via the Agency's own actions, such as the development of BACPAC to address drug substances and SUPAC to address drug products; as well as the Agency's development of a separate set of GMPs for APIs and participation in the ICH Q7 effort to do the same.

2. Given the existence of both the SUPAC and draft BACPAC documents, we believe the proposed Rule and its Guidance document should contain references to both, as they address nearly identical issues. However, in a number of cases the proposed Rule and Guidance actually conflict with SUPAC and BACPAC. Therefore, we believe that all of the documents should be brought into agreement before adoption by the Agency, despite the lack of an approved BACPAC guidance.

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3. The proposed Rule and Guidance document are written entirely from the perspective of the NDA/ANDA sponsors. As an agent for DMF holders, we feel that DMF holders have not been adequately represented in the Agency's regulations and guidelines; and feel this situation should be remedied as quickly as possible, especially considering the popularity of "outsourcing" manufacturing today.

4. We were pleased to see that many speakers at the Public Meeting held in Gaithersburg on August 19th agreed with our contention with respect to the use of the term "validate". The term is used in the proposed Rule and Guidance document to essentially mean, "assess", which is different than its common use in industry. We believe this has the potential to cause enormous confusion, and therefore, propose the word "validate" be replaced with the word "assess".

5. Lastly, it is our feeling that the proposed Rule does not comply with the intent of Section 116 of FDAMA. It is our belief that FDAMA's intent was to provide regulatory relief, and a "new approach" to manufacturing changes was anticipated. However, the Agency, in this Rule, has proposed the same "risk-based" system of the past, with filing determined by the "potential impact of a change". Perhaps in the drug product world this is an acceptable approach. However, in the chemical bond making and breaking world of drug substance it is a deficient approach. The "actual", not the "potential", impact of a change is the key issue in the drug substance world. We believe a *data-driven* system is needed; one in which data is obtained and used to determine the impact of a change. If the data has shown the drug substance to be impacted, then a stricter filing mechanism should ensue; and if not, then a less stringent mechanism should be used. To implement this system we would recommend the use of "decision trees" as presented at the Public Meeting and in a variety of prior documents including our own 1996 publication regarding this issue. This system, appropriately implemented, should make any "risk" associated with a change essentially disappear, since the actual impact would be known and not an object of someone's opinion. Hence, it would not be possible to generate a list of major/minor changes and corresponding filing mechanisms, *a priori*. All changes, and especially process changes, need to be evaluated on a case-by-case-basis, and the data collected permitted to dictate the filing mechanism based on the observed or "actual" impact.

In closing, we would like to thank you again for permitting public comment on proposed rules and regulations such as this. If you desire further clarification on any of the points noted above, please feel free to contact us.

Sincerely,

Amanda J. Hall

Amanda J. Hall
Regulatory and Technical Affairs

cc: Arthur Fabian, Ph.D., Jeanne Rude

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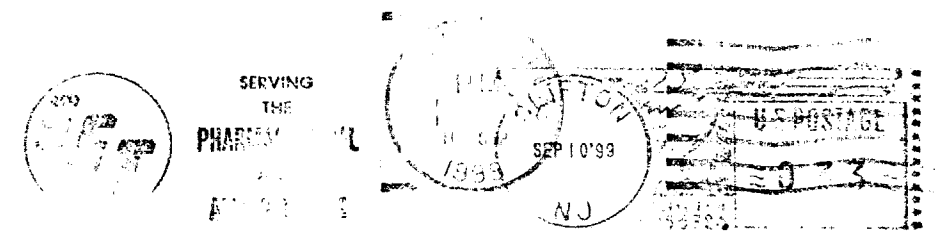


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